# Why do patients take herbs and nutritional supplements?

- **Dissatisfaction with conventional medicine**
  - > Relieve cancer-related symptoms
  - > Treat adverse effects of anticancer drugs
  - > Treat cancer
  - > Promote general well being
- **More active in own health care**
- **Philosophical orientations**

# Use in cancer survivors

- **54-81%: any vitamins or supplements**
- **26-77%: multivitamins**
- **Within first months of diagnosis**
- **Women**
- **Higher economic status**

**20-30% adverse effects < drug interactions**

**Concomitant use: growing concern**

# Communication disconnect

**38-85%: no consultation with physician**

- Physicians do not ask
- Physicians do not record
- Patients fear disapproval

# Drug interactions

- **Drug-drug**
  - > Food, nutritional supplements, formulation excipients, environmental factors
- **Interactions**
  - > Pharmacokinetics
    - Absorption, distribution, metabolism, elimination
  - > Pharmacodynamics
    - Similar molecular targets
    - Opposite effects
    - Similar effects

# Drug interactions: clinical relevance

**Depends on**

- **Co-administered drug**
  - > Dose, dosage regimen, therapeutic range
  - > Administration route, pharmacokinetics
- **Herb**
  - > Dose, dosage regimen
  - > Administration route
- **Patient**
  - > Genetic polymorphism
  - > Age, gender
  - > Co-morbid conditions

# Pharmacokinetics: absorption

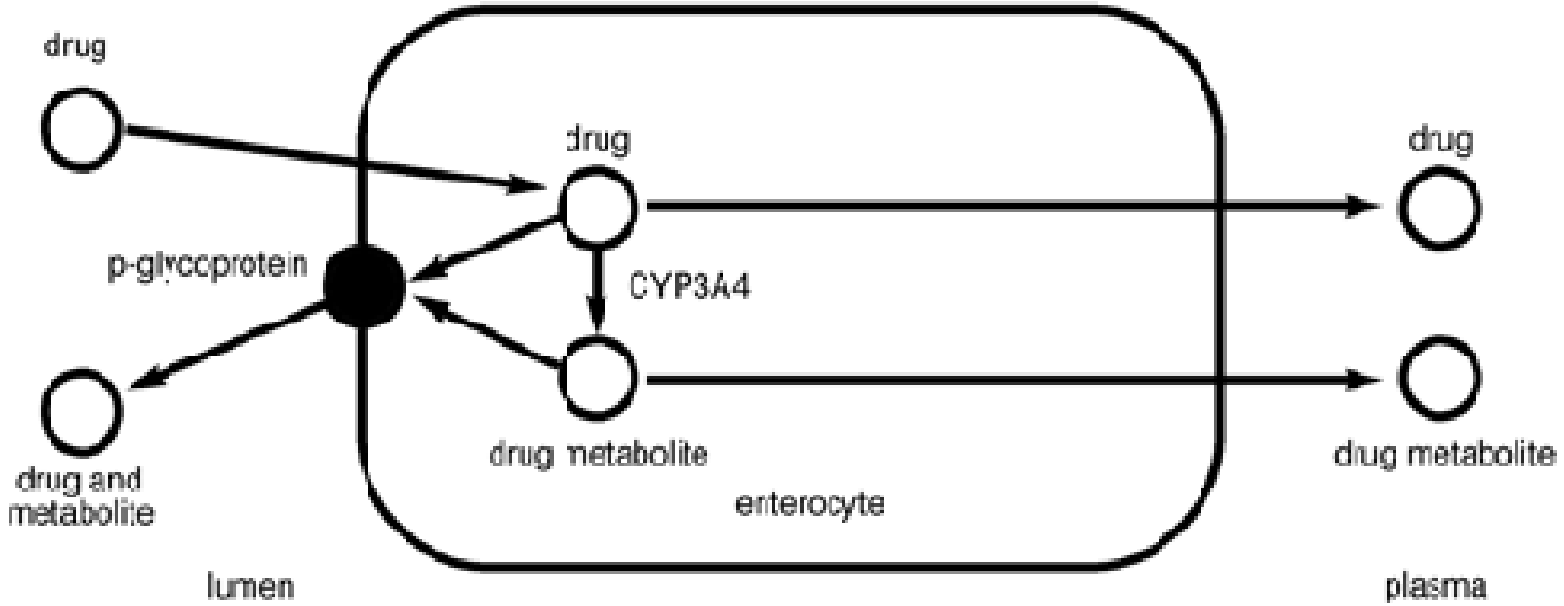
**Oral drugs and pro-drugs**

- **Food**
  - > Delays gastric emptying
  - > Raises intestinal pH
  - > Raises hepatic blood flow
  - > Slows gastrointestinal transit
- **Known drug interactions**
  - > Increases absorption erlotinib
  - > Decreases absorption capecitabine
  - > Delays absorption topotecan, fluorouracil

# Pharmacokinetics: absorption, metabolism, elimination

- **Cytochrome 450 family CYP450**
- **Drug transporters**
  - > Efflux: P-glycoprotein P-gP
  - > Influx: organic anion transporting polypeptide OATP

# Pharmacokinetics: absorption, metabolism, elimination



# Pharmacokinetics: absorption, metabolism, elimination

**The CYP family**

- **Metabolizes 60% of drugs**
  - > Biotransformation lipophilic substrates into hydrophilic metabolites
- **CYP3A4**
  - > Most abundant
  - > Liver, gastrointestinal tract
  - > Chemical carcinogenesis
- **Expression regulation**
  - > Hormones and nuclear receptors
    - Pregnane X receptor, constitutive androstane receptor, farnesol X receptor

# Pharmacokinetics: absorption, metabolism, elimination

**Anticancer drugs: substrates of CYP3A4**

- **Hormones**
  - > Anastrazole, letrozole, exemestane, tamoxifen
- **Tyrosine kinase inhibitors**
  - > Erlotinib, gefinitib, imatinib
- **Taxanes**
  - > Docetaxel, paclitaxel
- **Vinca alkaloids**
  - > Vinblastin, vincristin, vinorelbine
- **Topo-isomerase inhibitors**
  - > Doxorubicine, irinotecan, etoposide,teniposide
- **Alkylating agents**
  - > Cyclophosphamide, iphosphamide

# Pharmacokinetics: absorption, metabolism, elimination

- **P-glycoprotein P-gp**
  - > Encoded by multidrug resistance genes ABCB1
  - > Liver, kidney, intestines, brain, testis, uterus, adrenal gland, tumor cells
  - > Up-regulation by stress responses
    - Cytotoxic agents, heat shock, irradiation, inflammatory mediators, cytokines, growth factors
  - > Hepatic P-gp: 2.4 fold lower in women

# Pharmacokinetics: absorption, metabolism, elimination

- **Anticancer substrates of P-gP**
  - > Tyrosine kinase inhibitors
    - **Imatinib**
  - > Taxanes
    - **Docetaxel, paclitaxel**
  - > Vinca alkaloids
    - **Vinblastin, vincristin**
  - > Topo-isomerase inhibitors
    - **Doxorubicine, irinotecan, etoposide, teniposide, topotecan**

# Pharmacokinetics: absorption, metabolism, elimination

- **Organic anion transporting polypeptide OATP**
  - > Protein family
  - > Influx into plasma
  - > Regulated by small intestinal pH

# Pharmacokinetics: absorption, metabolism, elimination

**Herbal supplements: brand specific effects**

- **Garlic**
  - > Inhibition of CYP3A4, inducer in very high doses
- **Gingko**
  - > Inhibition of CYP3A4, inducer of CYP2C19
  - > CYP2C19 substrates: letrozole, gefinitib
- **Valerian**
  - > Inhibition of CYP2C19 , CYP2D6
  - > CYP2D6 substrate: tamoxifen

# Pharmacokinetics: absorption, metabolism, elimination

- **Echinacea**
  - > Inhibitor intestinal CYP3A4
  - > Inducer CYP3A4
- **Ginseng**
  - > Moderate inhibitor hepatic CYP3A4
- **Grape seed**
  - > In high doses: inducer of hepatic CYP3A4
- **Kava**
  - > Pregnane X receptor activator
- **St John's Worth**
  - > Potent inducer of CYP3A4 and P-gp
  - > Activator pregnane X receptor

# Pharmacokinetics: absorption, metabolism, elimination

- **Grape fruit**
  - > Potent inhibitor intestinal CYP3A4
  - > inhibitor P-gp and OATP
- **Black pepper**
  - > Inhibitor of CYP3A4, P-gp
- **Seville orange**
  - > Inhibition of CYP3A4, P-gp, OATP
- **Goldenseal**
  - > Inhibition of CYP3A4, CYP2D6
- **No interaction with**
  - > Saw palmetto, black cohosh, cranberry, bilberry, milk thistle

# Pharmacokinetics: distribution

- **Binding properties**
  - > Albumin, alpha-1-acid glycoproteins, lipoproteins, immunoglobulines, erythrocytes
- **Highly bound anticancer drugs**
  - > Paclitaxel, etoposide
- **Competitive binding with albumin**
  - > Evening primrose

# Pharmacodynamics

- **Synergistic interactions**
  - > Leucovorin and 5-fluorouracil
- **Antagonistic interactions**
  - > Corticosteroids and IL-2
- **Additive interactions**
  - > Vinorelbine with previous or concurrent paclitaxel on neurotoxicity
- **Sequence-dependent interactions**
  - > Paclitaxel preceding doxorubicine on cardiotoxicity

# Drug interactions: clinical relevance?

- **Drugs: narrow therapeutic range**
- **Drugs: steep dose-response curve**
- **Potent inhibitor of inducer**
- **Metabolism and elimination: single pathway**
- **Interactions results in diversion into alternative pathway**

# Antioxidants and anticancer drugs

- **Lower antioxidant status**
  - > Cancer
  - > Anticancer treatment
- **Supplements**
  - > Selenium
  - > Vitamin C
  - > Sufficient fruit and vegetables

# Antioxidants and anticancer drugs

- **Antioxidants**
  - > Detoxifying free radicals
    - Inhibition of free radical intermediates
    - Mitomycin C, bleomycin
  - > Strong nucleophiles
    - Reducing adverse effects
    - Glutathion
    - Coenzyme Q10
- **High level antioxidant stress**
  - > Anthracyclines, alkylating agents, platinum, camptothecins, epipodophylotoxines

# Antioxidants and anticancer drugs

- **Vitamin E**
  - > Prevents peroxidation poly-unsaturated fat
  - > Evidence not strong
    - Radiation fibrosis
    - Mucositis chemotherapy
    - Cell growth inhibition by 5-FU
    - Pro-oxidant: cigarette smokers + fatty acid diet
  - > Avoid depletion
- **ß-Carotene**
  - > Few and fragmentary studies
  - > Beneficial during chemo- and radiotherapy?

# Antioxidants and anticancer drugs

- **Selenium**
  - > Selenoproteins: glutathion peroxidase
  - > Insufficient data
    - Adverse effect chemo- and radiotherapy
    - Cisplatin resistance in ovarian cancer
  - > Narrow dose range
- **Vitamin C**
  - > Excessive quantities: pro-oxidants
  - > High dose methotrexate + high dose vitamin C: renal insufficiency

**No data on survival**

# Conclusions

**Be aware**

- **Avoid**
  - > Grape fruit and St John's Worth
- **Caution with**
  - > Gingko, ginseng, echinacea, kava, grape seed: CYP3A4 substrates
  - > Gingko: letrozole, gefinitib
  - > Valerian (paroxetin, fluoxetin): tamoxifen
  - > Evening primrose: paclitaxel, bleomycin
- **No antioxidants**
  - > Mitomycin C, bleomycin
- **Avoid antioxidant depletion**
  - > Vitamin E

# Conclusions

- **Studies should specify**
  - > Dosage
  - > Duration
  - > Time interval
  - > Life style
  - > Exposure to carcinogens
- **In a well-defined population**